REMARKS

Introductory Comments

Applicants thank the Examiner for the courtesy of a telephonic discussion on April 14, 2009 with applicants' undersigned representative wherein the outstanding rejections were discussed in the context of the pending claims.

The Claim Amendments

Applicants have canceled claims 2, 4-6, 10, 11 and 21-25 without prejudice to or disclaimer of the subject matter therein. Applicants expressly reserve the right to pursue the subject matter of any canceled claim in a continuation application.

Applicants have amended claim 1 and withdrawn claim 20. In case linking claim 1 is found allowable, applicants request rejoinder of withdrawn claim 20 for further examination.

Applicants have amended claim 1 to more particularly recite the claimed invention. Specifically, applicants have inserted the structure of compound 181 in place of the genus of Formula (A). Support for this amendment is found throughout the specification and claim 1 as originally filed. Applicants have amended claim 20 to more particularly recite the diseases intended. Support for this amendment is found throughout the specification as filed (e.g., page 56, paragraph [0060-0061]) and claim 21 as originally filed.

Applicants note that these amendments are made solely to expedite prosecution rather than for any reason related to patentability of the claims.

These amendments add no new matter. Their entry is requested.

The Rejections

35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 1, 2, 4-6, 10, 11 and 22 under 35 U.S.C. § 103(a) as being unpatentable over Montgomery (US 4,210,745) (hereinafter "Montgomery") in view of Stamos et al. (WO 00/56331) (hereinafter "Stamos") for the reasons of record as set forth in the Office Action dated February 14, 2008. According to the Examiner, applicants' anti-cancer data demonstrating surprising and unexpected synergistic rather than additive results and arguments to overcome this rejection were not persuasive. Specifically, the Examiner asserts the data is unpersuasive because "the applicants' claims do not recite the exact

individual amount of (a) fludarabine, and the exact individual amount of (b) a compound of formula A; is combined to produce an unexpected synergistic result." Applicants respectfully traverse for the reasons of record and for at least the following reasons.

First, as discussed *supra*, claims 2, 4-6, 10, 11 and 21-25 have been canceled. Therefore, this maintained rejection is moot with regard to claims 2, 4-6, 10, 11 and 22.

Second, as discussed in the applicants previous response (e.g., see page 11 of Reply filed July 29, 2008, hereinafter the " '08 Reply") Montgomery and Stamos do not teach or suggest the claimed combination of the present invention; namely the use of the IMPDH inhibitor compound 181 in combination with an apoptosis inducing, anti-cancer and anti-metabolite agent such as fludarabine. Montgomery teaches a procedure for preparing the anti-cancer agent fludarabine. Stamos teaches a genus of IMPDH inhibitors of formula A useful to treat cancers and tumors either alone or in combination with an additional anti-cancer agent. However, the specific combination of fludarabine with compound 181 is neither taught nor suggested by Montgomery or Stamos. Therefore, one skilled in the art would not have been motivated nor would have found it obvious to make the synergistic combination of the present invention based on the species disclosed in Montgomery and the genus and combination disclosed in Stamos.

Third, applicants have amended claim 1 to recite a composition directed to a specific combination of fludarabine plus compound 181 (rather than a compound of the genus of Formula A). Moreover, as discussed previously (e.g., see pages 11-12 of the '08 Reply), applicants have provided data (see, specification, Example 1, paragraphs [0065] to [0069] at pages 58-59) for the specific combination of compound number 181 either alone or in combination with fludarabine to evaluate the apoptotic effect (measured by percent apoptosis) on a Daudi cancer cell line. Additionally, as suggested by the Examiner, applicants provide herewith a more comprehensive presentation and explanation of this synergistic data in ¶¶ 7 and 8 of the §1.312 declaration by Jugnu Jain filed herewith (hereinafter "the Jain declaration").

Specifically, Figure 1 (reproduced at ¶ 7 of the Jain Declaration) showing the percent apoptosis against the concentration of compound 181 alone, fludarabine alone, and a combination of both agents is described in further detail. Therein, the combination of compound 181 and fludarabine results in a much greater percent apoptosis due to the synergy therebetween. (Id. at ¶ 7).

Similarly, Figure 2 (reproduced at ¶ 8 of the Jain Declaration) providing a graphical representation of the strong synergistic effect observed with the fludarabine/compound 181 combination is described in further detail. Therein, a CalcuSyn analysis of percent apoptosis shows a strongly synergistic effect at all three doses tested namely, the ED50, ED75 and the ED90. (Id. at ¶ 8).

Fourth, applicants disagree with the Examiner's assertion that in order to support the claim of unexpected and synergistic activity, applicants must claim "the exact individual amount of (a) fludarabine and the exact individual amount of (b) a compound of formula A". Applicants are aware of no such requirement either in the MPEP or in the case law that mandate specific dosages in a claimed combination to support a showing of surprising and unexpected activity. Applicants have demonstrated surprising and unexpected synergistic activity for the claimed combination at particular *in vitro* concentrations in the specification as filed and as discussed in the Jain Declaration. Applicants believe that this unexpectedly synergistic data alone should support a finding of nonobviousness of the present claims over those of Montgomery in view of Stamos.

Moreover, applicants have provided general dosage guidance for patients in the specification as filed (e.g., see paragraphs [0054] to [0055] at pages 53-54). As discussed therein, the amount of active ingredients (e.g., fludarabine and compound 181) in a particular dosage "will vary depending on the host treated and the particular mode of administration." Therefore, to recite a dosage with any more particularity in claim 1 (as suggested by the Examiner) would unfairly deprive applicants of the full scope of their invention.

In summary, the present invention provides a claimed combination of compound 181 and fludarabine that is neither taught nor suggested by Montgomery or Stamos. Furthermore, the unexpected synergistic effect (as opposed to merely additive) and the enhanced anti-cancer profile possessed by the claimed combination renders it non-obvious over Montgomery in view of Stamos. Accordingly, applicants respectfully request that the Examiner this § 103(a) rejection.

Non-statutory Double Patenting

The Examiner has again rejected claims 1, 2, 4-6, 10, 11 and 22 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 1-11 of

U.S. Patent No. 6,498,178 (hereinafter the "'178 patent"). Applicants respectfully traverse for the reasons of record and based on the synergistic data explained in detail in ¶¶ 7 and 8 of the accompanying Jain declaration.

Additionally and as discussed *supra*, claims 2, 4-6, 10, 11 and 21-25 have been canceled. Therefore, this maintained rejection is moot with regard to claims 2, 4-6, 10, 11 and 22.

Also, as discussed in the § 103(a) rejection section *supra*, the combination in claim 1 of the present invention is a non-obvious patentable invention over Montgomery and Stamos because it provides an unexpected synergistic effect resulting in an enhanced anti-cancer profile. By analogy, the presently claimed synergistic combination is an unobvious, patentable invention over the '178 patent because the '178 patent provides no teaching, suggestion or motivation to select the claimed combination and expect it to have this synergistic anti-cancer effect. Moreover, the Manual of Patent Examination Procedure (MPEP) states that "[a] double patenting rejection of the obviousness-type>, if not based on an anticipation rationale,< is 'analogous to [failure to meet] the nonobviousness requirement of 35 U.S.C. 103' " (see MPEP § 804 II.B.1 quoting *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). The MPEP further states that "[t]herefore, *>the< analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination" (see MPEP § 804 II.B.1 quoting *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985)). The relevant factual inquiries are as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) and include any objective indicia of non-obviousness. Importantly, if these indicia include evidence that the compounds possess superior and unexpected properties then such a showing should be sufficient to rebut a *prima facie* case of obviousness whether related to a § 103 rejection or a nonstatutory obviousness-type double patenting rejection.

Therefore, for all the reasons of record and those presented above, the present application is an unobvious, patentable invention over the '178 patent. Accordingly, applicants respectfully request that the Examiner withdraw this nonstatutory obviousness-type double patenting rejection over the '178 patent.

Conclusion

Applicants respectfully request that the Examiner consider the foregoing remarks and allow the pending claims to pass to issue.

Respectfully submitted,

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